UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/256,237	02/24/99	HEIDTMANN H	026083/0195

HM12/1010

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EXAMINER	
DAVIS, M	
ART UNIT	PAPER NUMBER
1642	18

DATE MAILED:
10/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/256,237	Heidtmann et al
Examiner	**Art Unit**
MINH TAM DAVIS	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 27, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *19-25* is/are pending in the application.

4a) Of the above, claim(s) *19, 20, 22, and 24* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *21, 23, and 25* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s): *2 sheet*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 21, 23, and 25 are being examined.

The following are the remaining rejections.

It is noted that rejection under 101 is withdrawn, in favor of rejection under 112, first paragraph, lack of enablement for use of the claimed polypeptide in treating diseases.

RESTRICTION

Applicant again asserts that it is mandated by MPEP 821.4 and the USPTO procedure, that claim 19 should be rejoined with group III, upon the allowability of claim 25.

It is noted that Applicant probably inadvertently recited group III, instead of group II. For the purpose of examination, it is assumed that Applicant requests rejoining of claim 19 of group III with the elected group II. This request is rejected because claim 19 is related to the claims of group II, as product and process, and further because the scope of claim 19 is different from that of group II. Although in the present application, the claims of group II are rejected under 35 USC 101, utility, and 112, first paragraph, enablement, for the use of the claimed product, the scope of

the utility rejection is different from the scope of the enablement rejection of claim 19, wherein the utility requirement is met when only a single use of the claimed compound is shown to be credible, specific, and substantial.

PRIORITY DATE

The Office acknowledges receiving a certified and translated copy of the parent case German Patent No. 19701141.1.

INFORMATION DISCLOSURE STATEMENT

It is noted that the information disclosure statements received on July 31/01 and August 03/01 are duplicates.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH, NEW REJECTION

Claims 21, 23 and 25 are indefinite, because the amended claim 25 is confusing. It is not clear whether a polypeptide encoded by the DNA sequence in item d) is bound to the active compound via a peptide bond, besides being bound to the active compound via a cleavable amino acid sequence, or whether a polypeptide encoded by the DNA sequence in item d) is bound to the active compound via a peptide bond of the cleavable amino acid sequence.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, NEW MATTER, NEW REJECTION

Claims 21, 23, 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The amended claim 25 is drawn to a polypeptide encoded by a nucleic acid construct, comprising at least one DNA sequence encoding a polypeptide, which is bound "by a peptide bond" to an active compound by an amino acid sequence cleavable by a protease, and inhibits the activity of said active compound, and wherein the nucleic acid encoding the clevable amino acid sequence does not naturally occur as operably linking the inhibiting nucleic acid sequence to the nucleic acid sequence encoding the active compound.

The specification only discloses a polypeptide encoded by a nucleic acid construct, comprising at least one DNA sequence encoding a polypeptide, which is bound to an active compound via an amino acid sequence cleavable by a protease, and inhibits the activity of said active compound, and wherein the nucleic acid encoding the clevable amino acid sequence does not naturally occur as operably linking the inhibiting nucleic acid sequence to the nucleic acid sequence encoding the active compound. The specification does not disclose a polypeptide encoded by a nucleic acid construct, comprising at least one DNA sequence encoding a polypeptide, which is bound "by a peptide bond" to an active compound by an amino acid

sequence cleavable by a protease, and inhibits the activity of said active compound, and wherein the nucleic acid encoding the clevable amino acid sequence does not naturally occur as operably linking the inhibiting nucleic acid sequence to the nucleic acid sequence encoding the active compound.

REJECTION UNDER 35 USC 101, UTILITY

Rejection under 35 USC 112, first paragraph of claims 21, 23, 25 pertaining to lack of credible and specific utility remains for reasons already of record in paper No.11.

Applicant asserts that specific utility is met, because the biological activity identified is the initiation of coagulation, and the therapeutic application is the deprivation of blood flow to tumor.

Concerning credible utility, Applicant recites MPEP 2107.01 and case law recited in MPEP 2107.01, asserting that the Office must establish through evidence that it is more likely than not than one of skill in the art would doubt the truth of the statement of utility. Applicant asserts that the Examiner acknowledges that the polypeptides are not activated everywhere in the body of a patient, but only at the site of the release of the protease, which in this case is the tumor.The Examiner, citing Denmeade et al, also acknowledges that the release protease (PSA in this case) is initially active and only subsequently becomes inactivated. Denmeade et al suggest that this short window of activity of the protease, PSA, in the vicinity of the tumor can be used for the selective activation of the peptide-coupled prodrugs to treat metastatic prostate cancer, i.e.

they propose exactly the type of utility for protease activable polypeptide that is asserted in the present application. Thus the reference recited by the Examiner actually substantiate the credibility of the asserted utility.

Applicant submits EXHIBIT A, reciting specifically Gilgenkrantz et al, 1986, and Leytus et al, 1986, which teach that the factor X precursor has been known since 1986, wherein the precursor is converted to a mature two-chain form by the excision of the tripeptide RKR. Example 1 and figure 3 in the specification show the replacement of Arg at amino acid position 195 with Tyr, thereby converting the natural cleavage site of factor X into a cleavage site that is specifically recognized by PSA.

Further, Applicant recites MPEP 2107.02(I), arguing that it is unnecessary for Applicant to prove that there would be sufficient coagulation to inhibit growth of new blood vessels in the tumor; there is a reasonable correlation between localized coagulation and the inhibition of angiogenesis.

In addition, Applicant recites MPEP 2107.02(IV), which quotes *Ex parte Balzarini*, arguing that specific disclosure of dosage and schedule treatment would require the completion of phase-III clinical trials, and that human clinical data is not required to demonstrate the utility of the claimed invention.

Concerning lack of utility if the target cells had an alternative means of survival, Applicant asserts that if the claimed compound restricted blood flow to a tumor and if the tumor had an alternative means of survival that could be stopped by a second, non-claimed compound;

both compounds would have utility even though neither compound on its own could destroy the tumor.

Moreover, concerning factors that could potentially have an adverse effect on successful therapy, including biological stability, half-life, clearance from the blood, degradation, immunological activation, inability to penetrate tissues or cells, absorption, and insufficient circulation in the target area to carry the formulation in appropriate concentrations, Applicant argues that this is not Applicant's burden to to provide guidance on these issues, once Applicant has asserted a specific utility, and it is presumed valid. The Exmainer has merely listed these factors, and offered nothing to suggest that any of them would have a significant adverse effect on the therapies contemplated by the claimed invention.

Applicant concludes that in view of the teaching in the specification, the publication recited by the examiner, and evidence submitted as EXHIBIT A, the utility of the claimed polynucleotide is credible.

Applicant's arguments set forth in paper No.14 have been considered but are not deemed to be persuasive for the following reasons:

The recitation of MPEP 2107.01, MPEP 2107.02(I) and (IV) and the submission of EXHIBIT A are acknowledged.

Denmeade et al teach a peptide HSSKLQ which is a substrate specific for PSA, hydrolyzed by homogenates of prostate tumor cells PC-82, and is stable in human sera. Although Denmeade et al speculates that said peptide could be used as a carrier to target products

for activation within sites of metastatic prostate cancer producing enzymatic active PSA, Denmeade et al also teach that the PC-82 xenograft model can be used for testing whether therapeutic prodrug activation is possible *in vivo*, and that the efficacy of the claimed peptide against PC-82 tumors *in vivo* will evaluated (p.4929, second column, last paragraph). In other words, since Denmeade et al teach that the prodrug activation *in vivo* and tumor cell killing *in vivo* are to be tested and evaluated, and in view of the unpredictability of cancer treatment, as overwhelmingly evidenced by Gura et al, Jain et al, Curti et al, and Hartwell et al (of record), one of skill in the art would have expected that the claimed *in vivo* prodrug activation and tumor cell killing are unpredictable. Further, although PSA is enzymatically active in extracellular fluid, once in the serum, PSA is no assayable enzymatic activity (Denmeade et al, p.4929, second column, first paragraph), and thus it is unpredictable whether PSA has any assayable enzymatic activity in the serum even for a short time, unless tested. Morover, even if PSA has a short window of activity in the serum, it is unpredictable that said short window of activity is adequate for cleaving a reasonable amount of the claimed polypeptide to be effective against tumors. Moreover, as shown in table 3, p.4926, in the reference by Denmeade et al, different substrate peptides for PSA have different levels of stability in various sera. Thus it is unpredictable that the claimed substrate peptide Arg-Lys-Tyr for PSA is stable *in vivo*. Further, since Applicant has not shown the utility of the claimed construct, it is Applicant's burden to provide guidance on the issues such as factors that could potentially have an adverse effect on successful therapy, including biological stability, half-life, clearance from the blood, degradation, immunological

activation, inability to penetrate tissues or cells, absorption, and insufficient circulation in the target area to carry the formulation in appropriate concentrations. Therefore, in view of the above, there is no correlation between *in vitro* assays and *in vivo* treatment in the instant application. Applicant however, has shown only that in *in vitro* conditions, transduced HEK 293 cells express mutated factor X, which in the added presence of PSA, counterbalances the coagulation defect of FX-deficient plasma.(Example 2). There is no disclosusre of *in vivo* tumor treatment.

Moreover, MPEP 2107.02 teaches that if reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or for testing an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process. In the instant application, since there is no correlation with therapeutic utility, the data generated *in vitro* could not be used to establish therapeutic or pharmacological utility.

Further, MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In

constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling." There is overwhelming evidence in the art that treatment of cancer is unpredictable, as taught by Gura, Jain, Curti, and Hatrwell (of record). However, the specification lacks guidance on necessary dosages and treatment schedules for successful using of the claimed constructs in the *in vivo* treatment of cancer.

Concerning the alternative means of survival of tumors, since it is unpredictable that the claimed compound could be used for treating cancer, it is even more unpredictable that there exists a second, non-claimed compound that would work in synergy with the claimed construct.

Thus, although an example is not always required, in view of the unpredictability of cancer treatment, as overwhelmingly evidenced by Gura et al, Jain et al, Curti et al, and Hartwell et al (of record), further in view of the lack of a correlation between *in vitro* data and *in vivo* cancer treatment, and in the absence of sufficient guidance concerning dosage and treatment schedule to treat melanoma patients, it would be undue experimentation for one of skill in the art to practice the claimed invention. The same lack of correlation with *in vivo* treament, and lack of guidances on necessary dosages and treatment schedules apply as well to the claimed treatment of allergies, autoimmune diseases, infections, inflammation, transplant rejection, thrombosis, blood vessel occlusions, and tissue injuries, including injuries to the central nervous system and damage to the nervous system.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Rejection under 35 USC 112, first paragraph of claims 21, 23, 25 pertaining to lack of enablement for use of the claimed polypeptide remains for reasons already of record in paper No.11.

Applicant argues that with the withdrawn of the 101 rejection, the 112, first paragraph, enablement rejection should be withdrawn.

Applicant's arguments set forth in paper No.14 have been considered but are not deemed to be persuasive for the following reasons:

The same arguments under answers to arguments against 101 rejection apply here as well.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Rejection under 35 USC 112, first paragraph, of claims 21, 23, and 25 pertaining to lack of enablement for a polypeptide construct comprising an amino acid sequence cleavable by any protease remains for reasons already of record in paper No.11.

Applicant asserts that in the 101 rejection, the Examiner has asserted that most PSA is inactive in the serum, by complexing with a protease inhibitor, and that this same complexing apply as well to the claimed proteases other than PSA, such as cathepsin, plasminogen activator, etc.. Thus in view of the very arguments and evidence provided by the Examiner with respect to utility, the alleged activation of the polypeptides of the present invention appears highly unlikely. Rather, as evidenced by Denmeade et al, the polypeptide will only be cleaved and activated at the

site of the release of the respective protease, in the short time before the protease is inactivated by complexation with an inhibitor.

Applicant's arguments set forth in paper No.14 have been considered but are not deemed to be persuasive for the following reasons:

Applicant is reminded that this is 112, first paragraph, scope rejection, and that in the first line of the rejection in the Office action of paper No:8, on 08/31/00, the Examiner recited that that if Applicant could overcome the 112, first paragraph enablement, claims 21, 23, and 25 are still rejected under 112, first paragraph, scope, i.e. if the arguments in the 101, or 112, first paragraph rejection are overcome, and PSA or proteases in the serum are not inactive, even at the target sites. Further, as set forth in 101 rejection, based on the reference by Denmeade et al, it is unpredictable that the claimed polypeptide will be cleaved and activated at the site of the tumors.

Moreover, the claims are drawn to a construct having a sequence cleavable specifically by any protease released by any mammalian cells, at any sites, which are not even target sites, for example normal cells that release trypsin, or chymotrypsin. In other words, the construct will kill normal cells and not target tumor cells. Further, each protease has specific substrates, and non-specific substrates (Denmeade et al, p. 4925, last paragraph, bridging first paragraph of p.4930, of record), Applicant however has not shown which substrates could be used for the broadly claimed proteases.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE, NEW REJECTION

If Applicant could overcome the above 101 and 112, first paragraph rejections, claims 21, 23 and 25 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide encoded by a nucleic acid construct, comprising at least one DNA sequence encoding a polypeptide, which is bound to an active compound via an amino acid sequence cleavable by a protease, and inhibits the activity of said active compound, wherein the inhibiting polypeptide and active compound are a prepro-protein, and wherein the nucleic acid encoding the clevable amino acid sequence does not naturally occur as operably linking the inhibiting nucleic acid sequence to the nucleic acid sequence encoding the active compound, does not reasonably provide enablement for a polypeptide encoded by a nucleic acid construct, comprising at least one DNA sequence encoding a polypeptide, which is bound to an active compound via an amino acid sequence cleavable by a protease, and "inhibits the activity of said active compound", and wherein the nucleic acid encoding the clevable amino acid sequence does not naturally occur as operably linking the inhibiting nucleic acid sequence to the nucleic acid sequence encoding the active compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Clams 21, 23 and 25 are drawn to a polypeptide encoded by a nucleic acid construct, comprising at least one DNA sequence encoding a polypeptide, which is bound "by a peptide bond" to an active compound by an amino acid sequence cleavable by a protease, and inhibits the activity of said active compound, and wherein the nucleic acid encoding the clevable amino acid

sequence does not naturally occur as operably linking the inhibiting nucleic acid sequence to the nucleic acid sequence encoding the active compound.

Due to the indefinite language of claim 25, and for examination purposes, it is assumed that claims 21, 23 and 25 are drawn to a polypeptide encoded by a nucleic acid construct, comprising at least one DNA sequence encoding a polypeptide, which is bound to an active compound via an amino acid sequence cleavable by a protease, and inhibits the activity of said active compound, and wherein the nucleic acid encoding the clevable amino acid sequence does not naturally occur as operably linking the inhibiting nucleic acid sequence to the nucleic acid sequence encoding the active compound.

The specification discloses an example of a prepro-form of factor X, wherein the cleavage site RKR of the preprofactor X is replaced with a peptide sequence linker cleavable by PSA. It is well known in the art that after the cleavage of the site RKR, the prepro-factor X is converted to a mature form, which could be activated by the cleavage of the activation peptide by factor IXa.

The specification however does not disclose any other type of polypeptide that could inhibit the activity of the active compound.

It is not clear how, other than a prepro-protein, any active compound could be released from the inhibition by an inbibiting polypeptide, upon cleavage of a linker, which links the inhibiting polypeptide to the active compound. For example, it is not clear how an inhibition of the activity of an enzyme, which is inhibited by an enzyme inhibitor, is abolished upon cleavage of a linker, wherein the ezyme and the enzyme inhibitor are linked by a peptide linker. Since it is

well known in the art that an enzyme inhibitor would tightly bind to the inhibited enzyme, one of skill in the art would not have expected that cleavage of a linker would release the binding of the enzyme inhibitor and would abolish the inhibition by the enzyme inhibitor. In other words, it is not clear how the active compound would become active upon cleavage of the linker. Since it is not expected that the active compound would become active upon cleavage of the linker, it would have been undue experimentation for one of skill in the art to use the claimed compound.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

October 1, 2001

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